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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/679,580	10/06/2003	Usha Kasid	224378	8237

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EXAMINER	
HUMPHREY, DAVID HAROLD	
ART UNIT	**PAPER NUMBER**
1643	

DATE MAILED: 08/09/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/679,580	KASID ET AL.	
	Examiner	Art Unit	
	David Humphrey	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-41* is/are pending in the application.

4a) Of the above claim(s) *12-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *05/31/05;02/09/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicants' election of Group I, claims 1-11, with traverse in the reply filed on 06/22/06 is acknowledged.

The traversal is on the grounds that the nucleic acids of Group I, the polypeptides of Group II, and the antibodies of Group III, are not independent inventions because all make reference to SEQ ID NO: 2. Applicants further argue that likewise the method claims of Groups VII-XVI include reference to either of the nucleic acids, polypeptides or antibodies of Groups I, II, and II and therefore are not independent methods. Applicants further argue since all relate to SEQ ID NO:2, the Examiner can readily find whether there exist any nucleic acids, polypeptides or antibodies which encode, include or are made from SEQ ID NO: 2. Lastly, Applicants' argue that claims 2, 12, and 15 can be regarded as linking claims.

Applicants' arguments have been carefully considered but found not persuasive. While the nucleic acid of SEQ ID NO: 2 may encode the claimed polypeptide, nucleic acids and amino acids require separate database searches. Proteins and nucleic acids have substantially different physical, chemical, structural and functional properties. DNA, deoxyribonucleic acids are unbranched polymers composed of four subunits whereas polypeptides are a linear order comprised of 23 different amino acid residues. Contrary to Applicants' argument, claims 2, 12, and 15 are not linking claims as but are

drawn to patentably distinct nucleic acids, proteins and antibodies, respectively. See MPEP § 809.

2. Claims 1-41 are pending.

Claims 12-41 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 1-11 are examined on the merits.

Claim Rejections - 35 USC § 112, first paragraph

3. The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 3, and 6-11, are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The Written Description Guidelines for examination of patent applications indicates, "the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction

to practice, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical characteristics and/or other chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show applicant was in possession of the claimed genus. " (See MPEP 2164).

Claim 3 is drawn to an isolated nucleic acid molecule comprising a polynucleotide encoding a polypeptide wherein, except *for at least one conservative amino acid substitution*, said polypeptide has an amino acid sequence selected from the group consisting of amino acids from about 1-1297 of SEQ ID NO:2 and amino acids from about 2-1297 of SEQ ID NO: 2. Claims 6-11 in part read on the isolated nucleic acid of claim 3, a method of making a recombinant vector using the nucleic acid, a recombinant host cell produced using the nucleic acid, and a recombinant method of producing a polypeptide with the nucleic acid. Since there are no amino acid residues specified wherein the conservative substitutions should take place, the claims read on a genus of isolated nucleic acids encoding for a polypeptides that have between 1 and 1297 conservative amino acid substitutions. This is a very broad genus of nucleic acids.

A conservative amino acid substitution replaces one amino acid with another amino acid of similar chemical structure that may have no affect on protein function or could also inactivate the protein. The effect of an amino acid substitution depends on the role of the particular residue in the protein's activity. On a nucleic acid level, conservative amino acid substitutions can result from some types of missense

mutations. Missense mutations may not affect protein function, or they may cause partial or complete loss of protein function. The effect of missense mutations on protein function depends on which amino acid is changed and the nature of the change. For example, some amino acids, often those on the surface, are relatively insensitive to changes, whereas other amino acids, such as amino acids at the active site of the enzyme are very sensitive to changes. Some missense mutations are silent because they do not affect the function of the protein; others cause partial or complete inactivation of the proteins function. The affect of missense mutations depends on the nature of the amino acid substitution and the position of the change in the protein.

The specification provides no guidance of which amino acid residues encoded by the claimed nucleic acids can tolerate conservative substitutions and which are crucial for the biological activity of the protein. The specification discloses that computer programs such as DNASTAR software can be used to determine which amino acid residues can be substituted, inserted, or deleted without abolishing biological or immunological activity in proteins, see page 19, paragraph 61, lines 1-6. The specification also states that the number of amino acid substitutions a skilled artisan would make depends on many factors and that generally speaking the number of substitutions for any given peptide will not be more than 50, 40, 30, 25, 15, 10, 5, or 3, see specification, page 22, paragraph 69, lines 3-6. However, the specification only provides one species, SEQ ID NO: 1, as an isolated nucleic acid.

A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or of a recitation

of structural features common to the members of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 199 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). In Regents of the University of California v. Eli Lilly (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that, while applicants are not required to disclose every species encompassed by a genus, the description of the genus is achieved by the recitation of a representative number of species falling within the scope of the claimed genus.

The instant specification does not provide adequate written description to support the claimed genus. There is one species of isolated nucleic acids disclosed: SEQ ID NO: 1. However, the claims encompass numerous species that are not further described.

To provide adequate written description and evidence of possession of a claimed genus, pro-apoptotic fusion proteins, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only species present in the claims is SEQ ID NO: 1. There is no disclosure of any nucleic acids that encode for any proteins with at least one conservative amino acid substitution retaining biological activity. The disclosure of a single species may provide an adequate written description of a genus when the species disclosed is representative of the genus. However, the

claims encompass numerous species that are not further described. There is substantial variability among the species. The general knowledge and level of skill in the art do not supplement the omitted description, because *specific*, not general, guidance is what is needed. Therefore, one of ordinary skill in the art would not recognize from the disclosure that Applicants were in possession of the genus of isolated nucleic acids that encode for proteins with at least one conservative substitution from about amino acid 1-1297. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). As discussed above, the skilled artisan cannot envision the detailed nucleic acid sequences of the encompassed genus of nucleic acid sequences, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d

1016.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481 at 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

5. Claims 3, and 6-11, are rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for an isolated nucleic acid molecule encoding an amino acid sequence of SEQ ID NO: 2, does not reasonably provide enablement for just any isolated nucleic acid molecule encoding a polypeptide with *at least one conservative amino acid substitution* from about amino acids 1-1297 or about amino acids 2-1297. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir,1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to

practice the invention must not be undue experimentation. The key word is 'undue' not 'experimentation'. " (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the breadth of the claims, (2) the nature of the invention, (3) the state of the prior art, (4) the level of one of ordinary skill, (5) the level of predictability in the art, (6) the amount of direction provided by the inventor, (7) the existence of working examples, (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The nature of the invention and the breadth of the claims: The claims are drawn to an isolated nucleic acid molecule encoding a polypeptide wherein *except for at least one conservative amino acid substitution*, the polypeptide has an amino acid sequence selected from the group consisting of amino acids from about 1 to about 1297 and amino acids from about 2 to about 1297 of SEQ ID NO: 2. The claims further recite recombinant vectors and host cells as well as methods of making recombinant vectors and host cells using the recited nucleic acid. Therefore, the claims encompass a genus of isolated nucleic acids that encode polypeptides that can vary from SEQ ID NO: 2 with between 1 and 1297 conservative amino acid substitutions as well as recombinant vectors, and host cells employing those nucleic acids. Thus, the claims are very broad and do not recite a specific function or domain that must be conserved.

The state of the prior art and the level of predictability in the art: Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, the replacement of a single lysine at position 118 of the acidic fibroblast

growth factor by a glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological activity of the protein (see Burgess et al, Journal of Cell Biology Vol 111 November 1990 2129-2138). In transforming growth factor alpha, replacement of aspartic acid at position 47 with asparagine, did not affect biological activity while the replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen, see Lazar et al (Molecular and Cellular Biology Mar 1988 Vol 8 No 3 1247-1252).

The art teaches that amino acid substitutions can have dramatic effects on a protein folding as well as enzymatic activity. Ibragimova et al. (Biophysical Journal, Oct 1999, Vol. 77, pp. 2191-2198) teach that factors affecting protein folding and stability are governed by many small and often opposing effects and that even when the "rules" are know for altering the stability of a protein fold by the introduction of a single point mutation the result is not reliable because the balance of forces governing folding differs for different protein sequences, and that the determination of the relative magnitude of the forces governing the folding and stability of a given protein sequence is not straightforward (page 2191, first column, lines 12-17 and second column, lines 3-8).

Although biotechnology has made great strides in the recent past, these references serve to demonstrate exactly how little we really know about the art. Elucidation of the genetic code induces one to believe that one can readily obtain a functional synthetic protein for any known nucleic acid sequence with predictable results. The results of the construction of synthetic proteins remain very unpredictable as Burgess et al, Lazar et al, and Ibragimova et al conclusively demonstrate.

The amount of direction provided by the inventor and the existence of working examples: The specification asserts that SCC-112 nucleic acids and polypeptides that modulate apoptosis as well as a diagnostic target for detecting cancers, see page 1, paragraph 2. The specification further states the isolated nucleic acid encodes amino acids from about 1 to about 1297 and about 2 to about 1297. The specification does not reasonably provide enablement for isolated nucleic acids that encode polypeptides wherein except for at least one conservative amino acid substitution the polypeptide has an amino acid sequence selected from about 1 to 1297 and about 2 to 1297 of SEQ ID NO: 2. Neither the specification nor the claims recite any protein function that must be conserved. The specification provides no guidance as to which specific amino acids may tolerate substitutions and still retain protein function. Therefore, it is unclear which, if any, amino acid sequences less than 100% identical to SEQ ID NO: 2 would maintain the activities proposed in the specification. It would seem that specific function(s) would be required to make the nucleic acids which encode the SCC-112 protein useful for the applications disclosed in the specification, such as cancer diagnosis, modulating apoptosis, and therapies for Alzheimer's, see the specification, page 13, paragraph 40; page 14, paragraph 44; page 15, paragraph 46; and pages 16 and 17, paragraph 52. Since the amino acid sequence of a polypeptide determines its structural and functional properties, predictability of which changes can be tolerated in a polypeptide's amino acid sequence and still retain similar activity requires a knowledge of and guidance with regard to which amino acid or acids in the polypeptide's sequence, if any, are tolerant of modification and which are conserved and detailed knowledge of the ways in which the

protein's structure relates to its function. The specification provides essentially no guidance as to which of the infinite possible choices is likely to be successful.

From the discussion above, it is clear that the predictability of changes to the amino acid sequence is practically nil as far as biological activities are concerned. The specification fails to provide sufficient guidance to enable one of ordinary skill in the art to make and use the claimed nucleic acids in a manner reasonably correlated with the broad scope of the claims. Without sufficient guidance, the changes which must be made in the amino acid residues of SEQ ID NO: 2, which results in less than 100% sequence identity is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue.

Quantity of experimentation needed to make or use the invention based on the content of the disclosure: In view of the Wands factors considered above, one of ordinary skill in the art would conclude that making the isolated nucleic acids encoding polypeptides with at least one conservative amino acid substitution from about 1 to about 1297 or about 2 to about 1297 would require undue experimentation.

Conclusion

6. Claims 1, 2, 4, and 5 are in condition for allowance.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Humphrey whose telephone number is (571) 272-5544. The examiner can normally be reached on Mon-Fri 8:30AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

David Humphrey, Ph.D.

August 3, 2006

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER